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Review

Diphtheria – 'The strangling angel' of children

Roger W. Byard, MD, Forensic pathologist *

School of Medical Sciences, The University of Adelaide, Level 3 Medical School North Building, Frome Rd, Adelaide, 5005 South Australia, Australia

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ABSTRACT

Diphtheria, an acute infectious condition caused by *Corynebacterium diphtheriae*, was once a major killer of children. Although the mortality rates dropped dramatically in the mid-twentieth century, due to a combination of improved standards of living and immunization programs, outbreaks are still occurring. Two children, aged four and five years respectively, are reported to demonstrate characteristic features of lethal cases. Death in case 1 was due to an extensive upper airway pseudomembrane causing acute respiratory failure. The diagnosis of diphtheria was only made at postmortem. Death in case 2 was due to acute cardiac failure with heart block complicating diphtheria. Other mechanisms in fatal cases involve disseminated intravascular coagulation, renal and endocrine failure. Declining levels of immunity among adults has resulted in a change in the epidemiological pattern of the disease with an older age of victims in recent outbreaks. As a result of population shifts and failure to immunize children it is likely that forensic pathologists may see more cases of diphtheria in the future. Due to the rarity of cases in Western communities and atypical presentations, the diagnosis may only be established at autopsy.

1. Introduction

Diphtheria is an acute infectious condition caused by *Corynebacterium diphtheriae*, a toxigenic bacteria that lives as a commensal in the human pharynx. It was once a major killer of children occurring in epidemics that resulted in thousands of deaths.[1] The mortality rates began to drop in the twentieth century in countries where standards of living improved, and then dramatically fell once immunization programs were introduced.[1] However, despite these events it remains a significant pathogen in many parts of the world, even today.

Death occurs from a variety of mechanisms, however the name 'strangling angel' of children arose from the wing shaped pseudomembranes that form in the oropharynx. Dislodgment and impaction of these pseudomembranes caused acute airway obstruction and sudden death.[1,2] Given that there has been a resurgence of cases of non-lethal and lethal diphtheria in a number of countries in recent decades, and that considerable population displacements are occurring due to refugee and immigration movements, more cases may be encountered in forensic practice. The following review was undertaken, therefore, to highlight the pathological features of this 'forgotten' disease. To illustrate lethal manifestations in children two cases are also described.

2. Case reports

The pathology archives at The University of Adelaide, Australia, were searched for cases of lethal diphtheria. Two autopsy cases were located, the details of which are reported below.

Case 1: A four-year-old girl was admitted to hospital with a sore throat and respiratory distress. The presence of an exudate over her tonsils raised the possibility of diphtheria however microbiological cultures do not reveal *C. diphtheriae*. Despite antiobiotic therapy she died within 24 h of admission "in acute respiratory distress".

At autopsy the most striking findings were in the upper airway where yellow adherent material was present in the pharynx covering the tonsils. This was associated with cervical lymphadenopathy and a pseudomembrane which extended from the epiglottis throughout the entire larynx into the trachea and bronchi (Fig. 1). Histology showed desquamation of lining epithelium in the upper airway with extensive fibrinopurulent debris. Cervical lymph nodes were congested with necrotic germinal centers and the lungs were oedematous and haemorrhagic. A postmortem nasal swab grew *Corynebacterium diphtheria.* Death was due to acute respiratory failure complicating diphtheria. [Further images, but not pathological details, of this case have been published previously[3]].

Case 2: A five-year-old boy was admitted to hospital, ill with a sore throat. A grey membrane was present over his tonsils and the adjacent pharynx and *C. diphtheriae* was isolated on cultures. He was treated with antibiotics and diphtheria antitoxin but developed respiratory distress secondary to pseudomembrane formation

* Tel.: +61 8 8303 5441; fax: +61 8 8303 4408.
E-mail address: byard.roger@saugov.sa.gov.au.

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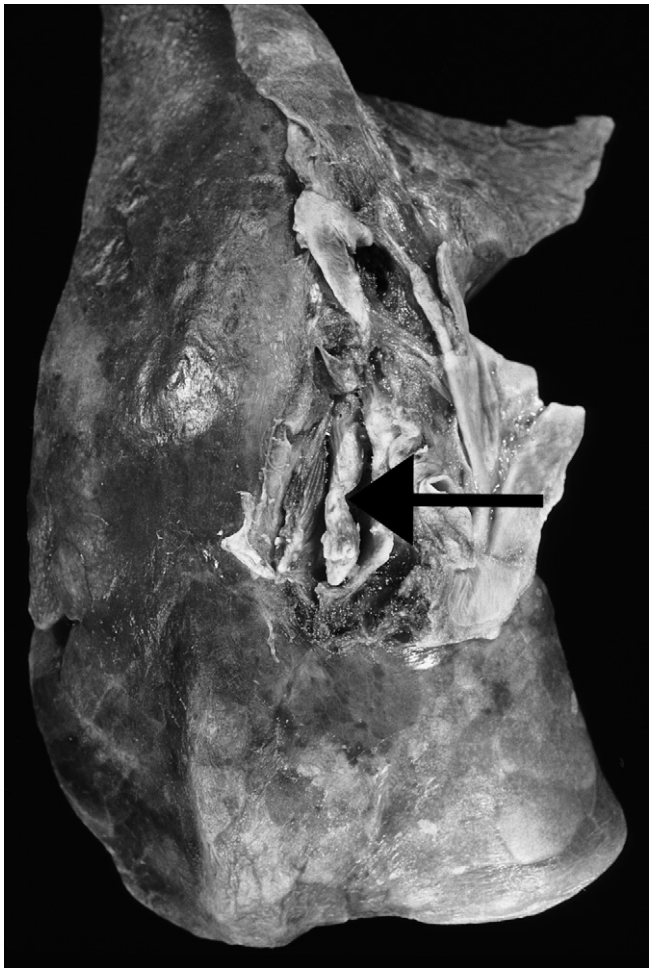

Fig. 1. Lung with an opened bronchus showing pseudomembranous occlusion (arrow) in a four-year old girl with diphtheria who died of acute respiratory distress.

and required a tracheostomy with ventilation. He then developed complete atrioventricular dissocation with right bundle branch block, but remained clinically stable. He died suddenly in the twelfth hospital day.

At autopsy there was evidence of cardiac failure with a pale and markedly dilated heart and bilateral straw-coloured pleural effusions. The tonsils were inflamed but without pseudomembranes. Death was due to acute cardiac failure complicating diphtheria.

3. Discussion

3.1. Historical perspective

Diphtheria was first recognized as a specific disease by Bretonneau in 1826 and named "la diphthérite" because of the leather-like exudate that formed in the oropharynx (Greek: leather = diptherа).[1] It was not until 1884 that Loeffler first identified *Corynebacterium diphtheria* as the causative agent.[4] At the time it was one of the most serious of childhood infections with one in 20 individuals in temperate climates having had the disease, with a mortality rate of 5–10%.[5] Seventy percent of those infected were aged less than 15 years.[6] Rural communities were the most vulnerable. In the 16th and 17th centuries in Spain diphtheria had been known as "morbus suffocans" or "garotillo"[7] and in the 18th century in the New England states of the US as "throat distemper".[8]

Dramatic declines in the incidence of diphtheria occurred following mass immunization campaigns in Western countries instituted in the 1940s and 1950s, although improved economic and living conditions (with smaller families and less crowding) had already led to a decline in numbers. For example, in Cracow, Poland between 1889 and 1909 the percentage of case of diphtheria in children under five years of age was 76%. This reduced to 43% between 1930 and 1932 without immunization campaigns.[6] The rate of diphtheria in Baltimore, US, in 1900 was 260 per 100,000, 124 per 100,000 in 1925 and 0 per 100,000 in 1960.[1] Transmission occurs by direct contact or by droplet infection from sneezing or coughing.[9]

3.2. Pathological effects

The pathogical consequences of diphtheria infection are caused by production of a potent toxin. The incubation period may be from one to eight days, but is usually between two to five days. The onset is often nonspecific with a lowgrade fever and a sore throat which may mimic streptococcal pharyngitis, candidiasis or infectious mononucleosis.[1,10,11] After about 24 h the pseudomembrane appears covering the soft palate, uvula and tonsils. This initially appears white but darkens as blood seeps into it. In young children a more severe form occurs known as malignant or "bull neck" diphtheria. The onset is abrupt and the growth of the pseudomembrane more rapid with involvement of the buccal cavity, entire pharynx, middle ear and nose.[1] The soft palate, uvula and tonsils may undergo necrosis and slough, and necrotic lesions may penetrate into the underlying skeletal muscle with marked hemorrhage.[9] More distal airway may have thinner pseudomembranes and the lungs are hemorrhagic and edematous.[12] Pseudomembranes may have an inner layer of fibrin with an outer coating of neutrophils with aggregates of embedded bacteria within the necrotic material.[9]

There is marked swelling of the cervical lymph nodes and adjacent soft tissues producing the characteristic "bull neck" appearance. Compression of the jugular veins may cause marked congestion of the face.[1] Other parts of the upper airway may be involved with nasal and laryngeal diphtheria, the latter associated with a high mortality rate.

The heart may have pale, dilated, chambers with a characteristic 'streaky" appearance. Histologic sections may show marked hyaline degeneration and necrosis with mononuclear cell infiltration and lipid vacuoles within surviving myocytes.[9] Adequate treatment requires rapid administration of diphtheria antitoxin and antibiotic coverage.[11] Superficial mucosal erosions may be present within the stomach and non-lethal diphtherial infections of the skin are found in the tropics, although these may lead to pharyngeal involvement through autoinfection.[2] Other sites of infection involve mycotic aneurysm formation, splenic abscess, osteomyelitis and septic arthritis.[4]

3.3. Lethal consequences

Death may be quite sudden and unexpected resulting from dislodgement or growth of pseudomembranes with acute obstruction of the upper airway as in case 1. Cardiac involvement occurs with both endocarditis and myocarditis being reported. Almost 50% of infected patients have some degree of cardiac impairment which has been shown in an animal model to be due to direct myotoxicity from the diphtheria toxin.[1] This may cause lethal heart block or cardiac failure[13] and may take a number of days to develop, as in case 2. Those with the most severe form of the disease develop myocarditis within the first few days of the illness.[1] Endocarditis most often involves non toxigenic strains and is associated with prosthetic valves or homografts.[4,14,15]

Diphtheria toxin also damages neural structures such as the anterior horn cells, dorsal root ganglia and cranial nerves with resultant paralysis, most often involving the palatal muscles. This may predispose to regurgitation of swallowed fluids through the nose[9] and aspiration from bulbar paralysis. Involvement of the muscles of respiration may cause respiratory failure.[16] All of the pathological effects of diphtheria have been reproduced in animal models by injecting the toxin.[1]

The mortality rate of diphtheria varies depending on age and sex, with young children historically being the most vulnerable. Girls are more susceptible to infection, however the fatality rate in boys is higher mostly due to their higher incidence of laryngeal involvement.[1] Other problems that may lead to death are disseminated intravascular coagulation, renal failure, and hypotension and endocrine failure associated with adrenal gland involvement[13] (Table 1).

3.4. Epidemiology

Diphtheria is vulnerable to elimination, as humans are the only reservoir, an effective vaccine exists and the seasonal incidence aids interruption of its transmission, but unfortunately eradication has not occurred.[7] The incidence and rate of diphtheria epidemics has varied between developed and developing countries, with the latter rarely having large scale outbreaks in the past.[6] This was considered due to the high rate of *C. diphtheria* skin infections which led to the development of early immunity. This situation has, however changed in recent years with outbreaks reported in several countries associated with high mortality rates involving older victims. For example, in Khartoum, Sudan, 50% of cases admitted to hospital in an outbreak in 1978 (pre-immunization programs) were children under the age of five years. This contrasted with an outbreak in 1988 when only 19% were under five years. Similar trends have been reported in Jordan, Algeria and Lesotho.[6,17]

The fall in numbers of cases of diphtheria in developed countries has also led to a reduction in numbers of individuals exposed to the organism and therefore in those with natural immunity. This has resulted in a declining level of immunity particularly in the adult population,[1] one effect of which was observed in the 1990s when outbreaks of diphtheria occurred in Russia and the Ukraine with increased numbers of infected adults.[6] In 1993 15,211 cases of diphtheria were reported in Russia and 2987 in the Ukraine. A major factor in these outbreaks was also reduced numbers of immunized children.[7]

One of the major risk factors for individuals living in developed countries is travel to an endemic country[11] and so a history of recent travel is important to elicit in the evaluation of possible cases. Others may be at risk from asymptomatic carriers if they have not been immunized.[18,19] While *C. diphtheria* is the major agent involved in lethal diphtheria, cases may also arise from *Corynebacterium ulcerans*, a toxin producing bacteria that is traditionally transmitted from farm animals through raw milk and dairy products, but which recently has been associated with domestic cats and dogs.[20–22]

Table 1
Potentially lethal consequences of infections with *Corynebacterium diphtheria*.

1. Upper airway obstruction
2. Myocarditis
3. Endocarditis
4. Heart block/acute cardiac failure
5. Palatal, pharyngeal and bulbar paralysis
6. Respiratory muscle paralysis
7. Miscellaneous: Disseminated intravascular coagulation and multiorgan failure

4. Conclusion

Recent outbreaks of diphtheria in a range of countries have demonstrated that incomplete population immunity and population movements may render communities vulnerable to this uncommon infection. As a result of population shifts and failure to immunize children it is likely that forensic pathologists may see more cases of diphtheria in the future. Due to the rarity of cases in Western communities, and atypical presentations, the diagnosis may only be established at autopsy, as in case 1.[23] A high index of suspicion needs to be maintained, therefore, in assessing possible cases so that forensic facilities are able to quickly inform public health authorities. This report demonstrates the range of manifestations that infections with *C. diphtheria* may have, possible lethal mechanisms that may lead to sudden and unexpected death, and recent changes in the epidemiology. The autopsy in suspected cases should include microbiological samples from the oropharynx and upper airway, in addition to extensive histological sampling of cardiac, neural, upper airway and lymphoid lesions.

Conflicts of interest
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